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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

SM -

Office Action Summary	Application No.	Applicant(s)	
	10/008,789	BENNETT ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10,12-15 and 19-22* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,12,15,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence search alignment*.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed May 24, 2004.

Claims 1, 2, 4-10, 12-15, and 19-22 are pending in the instant application. Claims 1 and 19 have been amended. Claims 21 and 22 have been withdrawn.

Claims 1, 2, 4-10, 12-15, 19, and 20 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed on February 23, 2004, claim 19 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicants Remarks and Amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new written description rejection.**

The instant claims read on a compound 8 to 50 nucleobases in length targeted to the 5'-untranslated region, the start codon region, the coding region, the stop codon region, or the 3'-untranslated region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3), with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3; wherein said compound specifically hybridizes with and differentially inhibits by at least 41% the expression of one or more of the variants of thyroid hormone receptor interactor 6 relative to the remaining variants of thyroid hormone receptor interactor 6.

The claimed invention encompasses any nucleic acid compound that specifically hybridizes to any variant of the thyroid hormone receptor interactor 6 gene, which includes sequences from mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth. The specification as filed provides only a description of the human thyroid hormone receptor interactor 6 gene represented by SEQ ID NO:3, and a variant of the human thyroid hormone receptor interactor 6 represented by SEQ ID NO:11.

The specification provides only antisense compounds complementary to target sites, or "active sites" (see specification page 83, lines 10-21) of the human thyroid hormone receptor interactor 6 mRNA molecule (SEQ ID NO:3), wherein such antisense compounds are effective to inhibit expression of the target sequence. Additionally, the specification provides only one antisense compound complementary to a target site, or "active sites" (see specification page 83, lines 10-21) of a variant of the human thyroid hormone receptor interactor 6 mRNA molecule

(SEQ ID NO:11), wherein such antisense compound is effective to inhibit expression of the target sequence. However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use human thyroid hormone receptor interactor 6 (SEQ ID NO:3, or a variant of human thyroid hormone receptor interactor 6 (SEQ ID NO:11) to predict the structures of antisense compounds complementary to target sites or "active sites" of thyroid hormone receptor interactor 6 isolated from other sources, including all polymorphic, allelic and splice variants of this mRNA.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of compounds that target human thyroid hormone receptor interactor 6 or a variant of human thyroid hormone receptor interactor 6, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claim Rejections - 35 USC § 102/Claim Rejections - 35 USC § 103

In the previous Office Action mailed on February 23, 2004, claims 1, 12, 19, and 20 were rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over

Murthy et al (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667). **This rejection is withdrawn in view of Applicants amendment** to the claims to recite the limitation, "with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3" in claim 1. In addition to amending the claims, Applicants argue that in rejecting the claims under 35 U.S.C. 102 and 103, a prima facie case established by the Examiner can be rebutted by evidence showing that the prior art product does not necessarily possess the characteristic of the claimed product. Applicants rely on MPEP 2112.01. Applicants contend that an oligonucleotide that is complementary to a target sequence does not necessarily inhibit expression of the target sequence. As evidence, Applicants direct the Examiner to Table 1 of the instant application where at least 5 of the antisense oligonucleotides, which are 100% complementary to the target sequence, do not have the function of inhibiting expression of the target sequence. Applicants contend that the oligonucleotide primer disclosed by Murthy does not necessarily possess the characteristics of the claimed invention.

Applicants arguments have been fully considered but are not found persuasive because the oligonucletoide primer disclosed by Murthy et al. is reverse complementary to nucleobases 1628-1603 of SEQ ID NO:3 of the instant invention. Referring to Table 1 of the instant specification, SEQ ID NOs: 70-72 contain overlapping regions of nucleobases 1628-1603 (e.g. nucleobases 1594-1642). It is noted that SEQ ID NOs: 70, 71, and 72 inhibit thyroid hormone receptor interactor 6 expression by 75%, 93%, and 91%, respectively. Given this high degree of inhibition of thyroid hormone receptor interactor 6 gene expression demonstrated by the instant specification, one skilled in the art would conclude that the oligonucletoide primer disclosed by Murthy et al. would undoubtedly inhibit thyroid hormone receptor interactor 6 gene expression.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 12, 14, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667). **This is a new rejection.**

Claims 1 and 20 are drawn to a compound 8 to 50 nucleobases in length targeted to the 5'-untranslated region, the start codon region, the coding region, the stop codon region, or the 3'-untranslated region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3), with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3; wherein said compound specifically hybridizes with said nucleic acid molecule encoding thyroid hormone receptor interactor 6 and inhibits the expression of thyroid hormone receptor interactor 6. Claims 2, 14, 12, 19 and 20 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations, wherein the compound is an antisense; wherein the

compound further comprises a pharmaceutically acceptable carrier or diluent; wherein said compound specifically hybridizes with and differentially inhibits by at least 41%.

Murthy et al. disclose an oligonucleotide primer of the following sequence: 5'-GCCCCGACATGGCCTGGAAAGG-3' (ZRP-R9), see page 20680, last paragraph. This oligonucleotide primer is reverse complementary to nucleobases 169-148 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the oligonucleotide primer disclosed by Murthy et al. and nucleobases 169-148 of SEQ ID NO:3 is contiguous as the local similarity is 100% and does not contain any mismatches. Given this high degree of similarity, the oligonucleotide primer disclosed by Murthy et al. meets all the structural requirements of the instant claims and would be expected to specifically hybridize to a nucleic acid encoding thyroid hormone receptor interactor 6, as per applicant's definition set forth in the specification as filed, pages 8 and 9, lines 12-37 and 1-8, respectively. Accordingly, the oligonucleotide primer disclosed by Murthy et al. would specifically hybridize to SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression by at least 41% under generally any assay conditions as recited in claim 19 falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705,

709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the oligonucleotide primer disclosed by Murthy et al. would or would not have the additional "functional limitation" of "inhibiting expression" of thyroid hormone receptor interactor 6 by at least 41% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 2, 12, 14, 19, and 20 are anticipated by Murthy et al.

Claims 1, 2, 12, 14, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al (Gene Expression, 1999 Vol. 8:207-217) [Applicants reference AE]. **This is a new rejection.**

Zhao et al. disclose an upstream adaptor primer of the following sequence 5'-GACGAATTCCGGGCCCACCTGGCTTC-3' (see page 208, second column, mid-column). This adaptor primer was used to create an expression plasmid for FLAG-tagged full length thyroid hormone receptor interactor 6 (Trip6) (amino acids 2-476) and corresponded to the 5' end of human Trip6 and contained a flanking *Eco*RI site and downstream T3 primer. Since the adaptor primer of Zhao et al. meets all the structural requirements of the instant claims, the

adaptor primer would also be expected to specifically hybridize to a nucleic acid encoding thyroid hormone receptor interactor 6, as per applicant's definition set forth in the specification as filed, pages 8 and 9, lines 12-37 and 1-8, respectively. Accordingly, the adaptor primer disclosed by Zhao et al. would specifically hybridize to SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression by at least 41% under generally any assay conditions as recited in claim 19 falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the oligonucleotide primer disclosed by Murthy et al. would or would not have the additional "functional limitation" of "inhibiting expression" of thyroid hormone receptor interactor 6 by at least 41% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 2, 12, 14, 19, and 20 are anticipated by Zhao et al.

Claims 1, 2, 12, 14, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Yi et al. (Genomics, 1998 Vol. 49:314-316) [Applicants reference AD]. **This is a new rejection.**

Yi et al. disclose an oligonucleotide primer of the following sequence: 5'-GCATTTGGTGACAAAGTCATACAGG-3' (ZRP-R9), see page 315, second column, last paragraph. This oligonucleotide primer is reverse complementary to nucleobases 1689-1665 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the oligonucleotide primer disclosed by Yi et al. and nucleobases 1689-1665 of SEQ ID NO:3 is contiguous as the local similarity is 100% and does not contain any mismatches. Given this high degree of similarity, the oligonucleotide primer disclosed by Yi et al. meets all the structural requirements of the instant claims and would be expected to specifically hybridize to a nucleic acid encoding thyroid hormone receptor interactor 6, as per applicant's definition set forth in the specification as filed, pages 8 and 9, lines 12-37 and 1-8, respectively. Accordingly, the oligonucleotide primer disclosed by Yi et al. would specifically hybridize to SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression by at least 41% under generally any assay conditions as recited in claim 19 falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or

substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the oligonucleotide primer disclosed by Yi et al. would or would not have the additional "functional limitation" of "inhibiting expression" of thyroid hormone receptor interactor 6 by at least 41% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 2, 12, 14, 19, and 20 are anticipated by Yi et al.

Claims 1, 2, 4-10, 12-15, 19, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Cowsert et al. [U.S. Patent No. 6,492,173]. **This is a new rejection.**

Claims 1, 2, 12, 19, and 20 are described above in the 35 U.S.C. 102(b) rejection against claims 1, 2, 12, 19, and 20 as being anticipated by Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) above. Claims 4-11, 13, and 14 are dependent on claim

1 and include all the limitations of claim 1, with the further limitations, wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide.

Cowsert et al. ('173) disclose an antisense oligonucleotide targeted to cyclin D2 with the following sequence: 5'-gcttgcgcaagatgtgct-3' (see SEQ ID NO:49). This antisense oligonucleotide targeted to cyclin D2 disclosed by Cowsert et al. comprise an internucleoside linkage, a modified sugar moiety, a modified nucleobase, or a chimeric oligonucletoide (see Cowsert et al. at columns 6-8). This antisense oligonucleotide is reverse complementary to bases 1518-1533 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the antisense oligonucleotide targeted to cyclin D2 disclosed by Cowsert et al. and nucleobases 1518-1533 of SEQ ID NO:3 is not contiguous as the local similarity is almost 94% and contains two mismatches (see attached sequence alignments). Given this high degree of similarity, the oligonucleotide primer disclosed by Cowsert et al. meets all the structural requirements of the instant claims and would be expected to specifically hybridize to a nucleic acid encoding thyroid hormone receptor interactor 6, as per applicant's definition set forth in the specification as filed, pages 8 and 9, lines 12-37 and 1-8, respectively. Accordingly, the antisense oligonucleotide disclosed by Cowsert et al. would specifically hybridize to SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression by at least 41% under generally any assay conditions as recited in claim 19 falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the oligonucleotide primer disclosed by Cowsert et al. would or would not have the additional "functional limitation" of "inhibiting expression" of thyroid hormone receptor interactor 6 by at least 41% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 2, 4-10, 12-15, 19, and 20 are anticipated by Cowsert et al.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed on February 23, 2004, claims 1, 2, 4-10, 12, 15, 19, and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937), and further in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is maintained** for the reasons of record set forth in the previous Office Action.

In response to this rejection, Applicants argue that the combination of prior art references do not teach all the limitations of the claims, there is no motivation to modify the references or combine the teaching to produce the claimed invention, and a reasonable expectation of success has not been established.

First, Applicants argue that claim 1 has been amended to recite, "with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3". Applicants contend that the prior art references cited by the Examiner do not teach or suggest the target site recited in claim 1 as amended. This argument has been considered but has not been found persuasive because nucleobases 1608 through 1642 comprise a very small portion of the 3'-untranslated region of a nucleic acid encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3). Given this proviso, the skilled artisan would be motivated to target the 5'-untranslated region, the start codon region, the coding region, or the stop codon region of a known target gene, such as thyroid hormone receptor interactor, as taught by Baracchini et al. (see column 9, lines 6-67 and column 10, lines 1-25).

Second, Applicants argue that the combination of art cited by the Examiner fails to render obvious the rejected claims because the references at best contain a generalized incentive to make antisense molecules against thyroid hormone receptor interactor 6, based on the discovery and characterization of thyroid hormone receptor interactor 6 protein as taught by Murthy et al. and a generalized teaching to make antisense targted to a "causative gene" as taught by Milligan et al. Applicants argue that the cited combination of art at best provides only a generalized incentive to make antisense compounds against thyroid hormone receptor interactor 6. Applicants further contend that the cited combination of prior art provides no teaching or suggestion to make specific antisense compounds. This argument has been considered but has not been found persuasive because Murthy et al. identify the structural domains of thyroid hormone receptor interactor 6 (also called ZRP-1), including the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region, and the region(s) involved in protein-protein interactions. Further, Murthy et al. also teach that the identification of other protein interacting domains is required for a better understanding of the role of ZRP-1 in cellular function. Milligan teach antisense techniques as a tool for probing the functions of individual genes. Milligan et al. further teach making an antisense oligonucleotide if the mRNA sequence (or cDNA) is known. Therefore, it would have been obvious to one of skill in the art to make the antisense oligonucleotides of the instant invention using the ZRP-1 sequence taught by Murthy et al. and following the method of Milligan et al. One skilled in the art would be motivated to make antisense targeted to thyroid hormone receptor interactor 6 to probe the function of thyroid hormone receptor interactor 6 in cellular processes. Furthermore, it is noted that there is no evidence of record to show any such differences between the thyroid hormone receptor interactor

6 (also called ZRP-1) sequence of Murthy et al. and SEQ ID NO:3 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to different sites/regions of thyroid hormone receptor interactor 6 of SEQ ID NO:3 of the instant invention. Regarding Applicants contention that the cited combination of prior art provides no teaching or suggestion to make specific antisense compounds, the instant application teaches making antisense compounds targeted to the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region of a nucleic acid encoding thyroid hormone receptor interactor 6. Murthy et al. teach the structural domains of thyroid hormone receptor interactor 6 (also called ZRP-1), including the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region, and the region(s) involved in protein-protein interactions. Further, the prior art suggests making antisense compounds targeted to the 5'-untranslated region, the start codon region, the coding region, or the stop codon region, of a known target gene (see Baracchini et al. at column 9, lines 6-67 and column 10, lines 1-25).

Third, Applicants argue that modifying or combining art to make out a prima facie case of obviousness requires that the prior art provide an ordinarily skilled artisan with a reasonable expectation of success in making the claimed invention. Applicant rely on MPEP 2143.02. Applicants contend that the cited references fail to provide a reasonable expectation of success. Applicants point to the Examiner to Milligan et al. who teach, "Although the field has progressed over the past decade, recent papers indicate that the observed activity of ODNs in tissue culture may be through non-antisense mechanisms (page 1923). This argument has been considered but has not been found persuasive because there is no evidence of record to show any such

differences between the thyroid hormone receptor interactor 6 (also called ZRP-1) sequence of Murthy et al. and SEQ ID NO:3 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to different sites/regions of thyroid hormone receptor interactor 6 of SEQ ID NO:3 of the instant invention. Further, regarding Applicants contention that Milligan et al. fail to provide a reasonable expectation of success, it is noted that Milligan et al. was published in 1993. A brief review of the first randomly chosen 10 patents issued to the assignee that published before Applicants filing date (i.e. 6,001,992, 6,124,133, 6,136,603, 6,140,124, 5,985,558, 6,020,199, 6,046,049, 6,133,032, and 6,140,126) reveals that each and every patent contains anywhere from a few to many oligonucleotides that inhibit target gene expression. Thus, the review described is more indicative of the current state of the art as a whole and more indicative of the true expectation of success. Accordingly, Applicants arguments have not been found persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
August 11, 2004

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Sequence search alignment...

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RESULT 745
AR266237/c
LOCUS       AR266237                 18 bp    DNA     linear   PAT 10-APR-2003
DEFINITION  Sequence 49 from patent US 6492173.
ACCESSION   AR266237
VERSION     AR266237.1  GI:29695083
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 18)
  AUTHORS   Cowsert,L.M.
  TITLE     Antisense inhibition of cyclin D2 expression
  JOURNAL   Patent: US 6492173-A 49 10-DEC-2002;
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                     /mol_type="genomic DNA"

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Qy       1518 GCACATCTTGTGCAAG 1533
              ||||||||||  |||||
Db         17 GCACATCTTGCGCAAG 2
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